REMARKS

1. Claims in the Case

Claims 1, 3, 5-7, 20, 22-53, 56-63 and 74-76 are canceled without prejudice. Claims 2, 8-13 and 54 are amended. Claims 10-19, 54 and 55 are withdrawn pending reintroduction. Claims 2, 4, 8-9, 21 and 64-73 are pending and under examination.

Applicants note that SEQ ID NOs 2-3 and 5-6 were rejoined by the Examiner.

2. Priority Claim

Applicants respectfully disagree with the Examiner's position with respect to priority. It is noted that PCT/US01/27692 (also known as WO 02/20726) does include a complete and enabling written description of the subject matter of the claims. We refer to the enclosed relevant pages of PCT/US01/27692; WO 02/20769 (filed 9/7/01), from which can be seen:

Current SEQ ID NO:1 is disclosed in the '769 application as SEQ ID NO:125

Current SEQ ID NO:2 is disclosed in the '769 application as SEQ ID NO:123

Current SEQ ID NO:3 is disclosed in the '769 application as SEQ ID NO:127

Current SEQ ID NO:4 is disclosed in the '769 application as SEQ ID NO:126

Current SEQ ID NO:5 is disclosed in the '769 application as the **bolded** sequence within SEQ ID NO:127, bottom of page 109 and the motif RECES is identified in **bold** as well in the middle of page 109.

Current SEQ ID NO:6 is similarly disclosed in the '769 application in the context of SEQ ID NO:127 as well.

There should be no question that the other aspects of the current claims are fully disclosed in the referenced parent PCT. We refer, for example, to the original claims from the '692 PCT (see enclosed pages 146-156 of the '692 PCT), with particular reference to claims 22 through 47.

3. Rejection of Claims 2, 4, 8-9, 21, 65-66, 68-69 and 70-73 as Anticipated over Marchio *et al.*

The Action next rejects claims 2, 4, 8-9, 21, 65-66, 68-69 and 70-73 over Marchio *et al.* ("Marchio") Applicants respectfully traverse.

First of all, it is noted that the only sequence disclosed by Marchio *et al.* is SEQ ID NO:2 (CPRECESIS). However, this sequence clearly in no way anticipates other sequences embraced by the claims, including, for example, SEQ ID NO:1 (CYNLCIRECESICGADGACWTWCAD GCSRSC), SEQ ID NO:3 (CPKVCPRECESNC) and SEQ ID NO:4 (CLGQCASICVNDC). The Action fails to explain, therefore, how Marchio anticipates claims 66 and 67. Reconsideration is requested.

Furthermore it is respectfully submitted that Marchio is not available as prior art under 35 U.S.C. §102(b). Applicant's undersigned representative verifies that he received, on October 8, 2007, the enclosed email communication from Ms. Mara Losi, an editor of the journal *Tumori*. In that communication, Ms. Losi confirmed that the issue of the journal *Tumori*, volume 86, No. 4 Suppl. 1, page 13 (2000), which included the abstract "Aminopeptidase A-binding peptides regulate endothelial cell function and inhibit angiogenesis," authored by Marchio *et al.*, was first publicly distributed in early October, 2000, to the attendees of the Congress of the Italian Cancer Society, October 5-7, 2000. This date is less than one year from the filing date of the PCT/US01/27692; WO 02/20769 (filed 9/7/01) as discussed above. Applicants therefore

respectfully submit that the subject Marchio publication is not available as prior art under 35 U.S.C. §102(b).

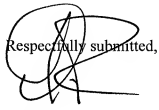
To further address any questions under 35 U.S.C. §102(a), Applicants enclose the declaration of the inventors, Drs. Pasqualini and Arap. There, Drs. Pasqualini and Arap declare that they are the sole inventors of the subject matter disclosed and claimed in the referenced application. They further declare that in connection with the studies reported in the Marchio *et al.* publication: a) S. Marchio was a Ph.D. student who assisted us in reducing the invention to practice; b) M. Trepel provided technical assistance in carrying out the described studies; c) R. Giordano provided technical assistance in carrying out the described studies; d) D. Valdembri provided technical assistance in carrying out the described studies; e) D. Nanus provided the APA transfected cells; and f) F. Bussolino was S. Marchio's Ph.D. advisor. They continue by declaring that foregoing individuals made no contribution to the conception of the present invention.

Drs. Pasqualini and Arap then continue by declaring that Wadih Arap was inadvertently not listed as an author on the Marchio *et al.* publication, and they conclude by confirming that to the extent that the Marchio *et al.* publication discloses aspects of the presently claimed invention, that Wadih Arap and Renata Pasqualini are the sole joint inventors thereof.

For the foregoing reasons, it is respectfully submitted that the subject claims have been shown to be free of the prior art.

5. Conclusion

In light of the foregoing, it is believed that the case is in condition for rejoinder of the withdrawn claims. If any questions arise, the Examiner is requested to contact the undersigned Applicant's representative.



Respectfully submitted,

David L. Parker
Reg. No. 32,165
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: December 12, 2007

Parker, David

From: Mara Losi [m.losi@pensiero.it]
Sent: Monday, October 08, 2007 9:31 AM
To: Parker, David
Cc: Serena Marchio
Subject: Tumori, 86 (suppl 1), N. 4, pag 13, 2000

Dear Mr. Parker:

I am the Editor for the journal Tumori. I can confirm that issue of the journal Tumori, volume 86, No. 4 Suppl. 1, page 13 (2000), which included the abstract "Aminopeptidase A-binding peptides regulate endothelial cell function and inhibit angiogenesis," authored by Marchio et al., was first publicly distributed in early October, 2000, to the attendees of Congress of the Italian Cancer Society, October 5-7, 2000.

Sincerely,

Mara Losi
Ufficio Editoriale Periodici
Il Pensiero Scientifico Editore
---
www.pensiero.it
Tel. 0686282331
Fax 0686282250
Via Bradano 3c
00199 Roma

fluid. Accordingly, elevated levels of VEGF (median 3560 pg/ml, range 287.9–24196 pg/ml), MMP2 & MMP9, both the proenzyme and the activated forms, were found in ascitic fluids of patients with ovarian carcinoma (n=28).

In conclusion, we show that high levels of soluble VEGF and MMP2, MMP9 are associated with ovarian carcinoma and disease progression.

AMINOPEPTIDASE A-BINDING PEPTIDES REGULATE ENDOTHELIAL CELL FUNCTION AND INHIBIT ANGIOGENESIS

S. Marchiò[1,2], M. Trepel[1], R. Giordano[1], D. Valdembri[2], D. Nanus[2], R. Pasqualini[1], F. Bussolino[2]

[1] The University of Texas MD Anderson Cancer Center; [2] Institute for Cancer Research and Treatment, University of Torino, Candiolo, Torino, Italy; [3] Memorial Sloan Kettering Cancer Center, NY, USA

Tumors depend on the recruitment of blood vessels for their growth. Endothelial cells in tumor blood vessels express angiogenic markers on their surface. Phage libraries can be generated to display up to 10^9 random peptide permutations on the minor coat protein pIII of bacteriophages, and are largely used to obtain defined peptide sequences interacting with a peculiar molecule. Peptides capable of homing to the vasculature of tumors have been identified in this manner. Such peptides have been associated with doxorubicin to achieve a targeted therapy. In other studies, peptides were linked to pro-apoptotic sequences, or were direct inhibitors of angiogenic molecules. In each approach, the inhibition of angiogenesis was coupled with a reduction of tumor growth, achieved by increased therapeutic efficacy and reduced toxicity.

Aminopeptidase A (APA, EC 3.4.11.7) has been shown to be overexpressed in angiogenic vessels. APA is a homodimeric, membrane-bound zinc metallopeptidase that hydrolyzes N-terminal Asp or Glu residues from oligopeptides. *In vivo*, APA is responsible for the conversion of angiotensin II into angiotensin III. The renin-angiotensin system plays an important role in regulating a large number of endocrine, cardiovascular and behavioral functions. Furthermore, recent studies have demonstrated an important role for angiotensins in angiogenesis.

A phage display library was screened on APA-transfected cells, selecting specific APA-binding motifs. A soluble peptide with the consensus sequence CPRECESIC was synthesized and proved to be a specific inhibitor of the enzyme activity, with an IC_{50}=800μM. The peptide was tested in proliferation and migration of endothelial cells challenged with VEGF-A. Both where inhibited by the peptide. The ability of endothelial cells to form capillary networks when plated on a matrix gel was impaired by CPRECESIC. *In vivo* angiogenesis in the CAM was also inhibited by about 50%.

Furthermore, preliminary studies revealed that APA-KO mice show impaired angiogenesis in the retina when challenged in the oxygen chamber assay. Our studies reveal an as yet unrecognized role for APA in angiogenesis and provide a tool for modulating such process. In addiction, APA-binding peptides also offer novel strategies for targeting tumor vasculature.

REDOX REGULATION OF BLADDER CANCER CELL ADHESION TO ECM PROTEINS

M. Mattioni[a], M. Cippitelli[a,*], A. Lupo[a], A. Santoni[a,a]

[a] Laboratory of Pathophysiology, Regina Elena Cancer Institute, Rome; *Department of Experimental Medicine and Pathology, La Sapienza University, Rome*

Redox status may influence tumor cell progression and metastatic ability. The effects of oxidant and antioxidant compounds on adhesion to extracellular matrix (ECM) proteins were investigated in a human bladder cancer cell line, EJ, as modulation of this function may influence tumor cell behaviour. Treatment of cells with antioxidants Pyrrolidinedithiocarbamate (PDTC, 60 μM) and Dithiothreitol (DTT, 500 μM) increased adhesion to Fibronectin (FN) and Collagen I (Coll I), whereas treatment with oxidant Phenylarsine oxide (PAO, 5 μM) completely inhibited adhesion to the same proteins. DTT is a dithiol antioxidant with closely spaced thiol pairs and PAO an oxidant selectively reactive with two thiol groups of closely spaced protein cysteinil residues; the binding is competitively reversed by DTT. In PAO-treated cells, DTT restored adhesion to FN and Coll I, inhibited by the oxidant. PDTC, a dithiol antioxidant structurally unrelated to DTT, was unable to reverse PAO inhibition of adhesion to Coll I.

To investigate the redox modulation of tumor cell adhesion, we studied the effects of oxidant and antioxidant compounds on actin stress fiber formation and focal adhesion assembly in cells bound to FN. We found that PAO (1 μM) inhibited the formation of focal adhesions, whereas PDTC and DTT increased the number of focal adhesions in spread cells; DTT reversed PAO induced effects on focal adhesion formation. Furthermore, PAO caused disappearence of actin stress fibers, whereas PDTC and DTT produced a thickening of actin fibers. DTT induced reappearence of actin stress fibers in cells treated with PAO.

These results further demonstrate a redox-sensitivity of tumor cell adhesion to ECM proteins.

THE Flk-1/KDR (VEGFR-2) RECEPTOR MEDIATES THE RESPONSE OF KAPOSI'S SARCOMA CELLS OF DIFFERENT ORIGINS TO HIV-TAT: A ROLE IN AIDS-KS PATHOLOGY

M. Morini, R. Benelli, S. Carlone, G. Arena, D.M. Noonan, A. Albini

Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

Kaposi's sarcoma (KS) is characterized by typical spindle shaped cells, an intense vascularization and an inflammatory infiltrate.

KS is linked to infection with the gammaherpesvirus

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Wadih Arap
Renata Pasqualini

Serial No.: 10/784,537

Filed: February 23, 2004

For: AMINOPEPTIDASE A (APA) TARGETING PEPTIDES FOR THE TREATMENT OF CANCER

Group Art Unit: 1648

Examiner: Li, Bao Q

Atty. Dkt. No.: UTSC:872US

DISCLAIMING DECLARATION OF RENATA PASQUALINI AND WADIH ARAP

Renata Pasqualini and Wadih Arap hereby declare as follows:

1. We are the sole inventors of the subject matter disclosed and claimed in the referenced application.

2. We understand that the PTO examiner in charge of this application has rejected various of the pending claims over the publication of Marchio *et al.*, *Tumori*, volume 86, No. 4 Suppl. 1, page 13 (2000), entitled "Aminopeptidase A-binding peptides regulate endothelial cell function and inhibit angiogenesis."

3. We are the sole inventors of the subject matter disclosed and claimed in the referenced application. In connection with the studies reported in the Marchio *et al.* publication: a) S. Marchio was a Ph.D. student who assisted us in reducing the invention to practice; b) M. Trepel provided technical assistance in carrying out the described studies; c) R. Giordano provided technical assistance in carrying out the described studies; d) D. Valdembri provided technical assistance in carrying out the described studies; e) D. Nanus provided the APA

transfected cells; and f) F. Bussolino was S. Marchio's Ph.D. advisor. The foregoing individuals made no contribution to the conception of the present invention.

4. Wadih Arap was inadvertently not listed as an author on the Marchio *et al.* publication. We hereby confirm that to the extent that the Marchio *et al.* publication discloses aspects of the presently claimed invention, Wadih Arap and Renata Pasqualini are the sole joint inventors thereof.

5. We hereby declare that all statements made of our own knowledge is true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date: Dec 6, 2007

Renata Pasqualini

Date: Dec 6, 2007

Wadih Arap

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(71) Applicant *(for all designated States except US)*: **BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM** [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARAP, Wadih** [BR/US]; 7171 Buffalo Speedway #328, Houston, TX 77025 (US). **PASQUALINI, Renata** [BR/US]; 7171 Buffalo Speedway #328, Houston, tX 77025 (US).

(74) Agents: **MALLIE, Michael, J.** et al.; Blakely, Sokoloff, Taylor & Zafman LLP, 7th floor, 12400 Wilshire Boulevard, Los Angeles, CA 90025 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HUMAN AND MOUSE TARGETING PEPTIDES IDENTIFIED BY PHAGE DISPLAY

(57) Abstract: The present invention concerns methods and compositions for in vivo and in vitro targeting. A large number of targeting peptides directed towards human organs, tissues or cell types are disclosed. The peptides are of use for targeted delivery of therapeutic agents, including but not limited to gene therapy vectors. A novel class of gene therapy vectors is disclosed. Certain of the disclosed peptides have therapeutic use for inhibiting angiogenesis, inhibiting tumor growth, inducing apoptosis, inhibiting pregnancy or inducing weight loss. Methods of identifying novel targeting peptides in humans, as well as identifying endogenous receptor-ligand pairs are disclosed. Methods of identifying novel infectious agents that are causal for human disease states are also disclosed. A novel mechanism for inducing apoptosis is further disclosed.

WO 02/20769 A1

Example 8. Identification of Receptor/Ligand Pairs: Aminopeptidase A regulates endothelial cell function and angiogenesis

Endothelial cells in tumor vessels express specific angiogenic markers. Aminopeptidase A (APA, EC 3.4.11.7) is upregulated in microvessels undergoing angiogenesis. APA is a homodimeric, membrane-bound zinc metallopeptidase that hydrolyzes N-terminal glutamyl or aspartyl residues from oligopeptides (Nanus *et al.*, 1993). *In vivo*, APA converts angiotensin II to angiotensin III. The renin-angiotensin system plays an important role in regulating several endocrine, cardiovascular, and behavioral functions (Ardaillou, 1997; Stroth and Unger, 1999). Recent studies also suggest a role for angiotensins in angiogenesis (Andrade *et al.*, 1996), but the function of APA in the angiogenic process has not been investigated so far.

In the present example, targeting peptides capable of binding APA were identified by screening phage libraries on APA-expressing cells. APA-binding peptides containing the motif CPRECESIC (SEQ ID NO:123) specifically inhibited APA enzyme activity. Soluble CPRECESIC (SEQ ID NO:123) peptide inhibited migration, proliferation, and morphogenesis of endothelial cells *in vitro* and interfered with *in vivo* angiogenesis in a chick embryo chorioallantoic membrane (CAM) assay. Furthermore, APA null mice had a decreased amount of retinal neovascularization compared to wild type (wt) mice in hypoxia-induced retinopathy in premature mice. These results may lead to a better understanding of the role of APA in angiogenesis and to development of new anti-tumor therapeutic strategies.

Materials and Methods

Cell cultures

The renal carcinoma cell line SK-RC-49 was transfected with an expression vector encoding full-length APA cDNA (Geng *et al.*, 1998). Cells were maintained in MEM (Irvine Scientific, Santa Ana, CA), supplemented with 2 mM glutamine, 1% nonessential amino acids, 1% vitamins (Gibco BRL), 100 U/ml streptomycin, 100 U/ml penicillin (Irvine Scientific), 10 mM sodium pyruvate (Sigma-Aldrich), and 10% fetal

calf serum (FCS) (Tissue Culture Biological, Tulare, CA). Stably transfected cells were maintained in G418-containing medium. HUVECs were isolated by collagenase treatment and used between passages 1 to 4. Cells were grown on gelatin-coated plastic in M199 medium (Sigma) supplemented with 20% FCS, penicillin (100 U/ml), streptomycin (50 μg/ml), heparin (50 μg/ml), and bovine brain extract (100 μg/ml). All media supplements were obtained commercially (Life Technologies, Inc., Milan, Italy).

Antibodies and peptides

The anti-APA mAb RC38 (Schlingemann *et al.*, 1996) was used to immunocapture APA from transfected cell lysates. CPRECESIC (SEQ ID NO:123) and GACVRLSACGA (SEQ ID NO:124) cyclic peptides were chemically synthesized, spontaneously cyclized in non-reducing conditions, and purified by mass spectrometry (AnaSpec San Jose, CA). The mass spectrometer analysis of the CPRECESIC (SEQ ID NO:123) peptide revealed six different peaks, possibly reflecting different positions of disulfide bounds and the formation of dimers. Due to the similar biochemical behavior of the different fractions on APA enzyme activity, a mix of the six peaks was used in all procedures described below.

APA immunocapture

Cells were scraped from semi-confluent plates in cold PBS containing 100 mM N-octyl-β-glucopyranoside (Calbiochem), lysed on ice for 2 h, and centrifuged at 13,000 x *g* for 15 min. Microtiter round-bottom wells (Falcon) were coated with 2 μg of RC38 for 4 h at room temperature and blocked with PBS/3% BSA (Intergen, Purchase, NY) for 1 h at room temperature, after which 150 μl of cell lysate (1 mg/ml) was incubated on the mAb-coated wells overnight at 4°C, washed five times with PBS/0.1% Tween-20 (Sigma), and washed twice with PBS.

APA enzyme assay

Cells and immunocaptured proteins were tested for specific enzyme activity according to Liln *et al.* (1998). Briefly, adherent cells or RC38-immunocaptured cell

extracts were incubated for 2 h at 37°C with PBS containing 3 mM α-L-glutamyl-p-nitroanilide (Fluka) and 1 mM $CaCl_2$. Enzyme activity was determined by reading the optical absorbance (O.D.) at 405 nm in a microplate reader (Molecular Devices, Sunnyvale, CA).

Cell panning

A $CX_3CX_3CX_3C$ (C, cysteine; X, any amino acid) library was prepared (Rajotte *et al.*, 1998). Amplification and purification of phage particles and DNA sequencing of phage-displayed inserts were performed as described above. Cells were detached by incubation with 2.5 mM EDTA in PBS, washed once in binding medium (DMEM high glucose supplemented with 20 mM HEPES and 2% FCS), and resuspended in the same medium at a concentration of $2x10^6$ cells/ml. 10^{10} TU of phage were added to 500 µl of the cell suspension, and the mixture was incubated overnight (first round) or for 2 h (successive rounds) at 4°C with gentle rotation. Cells were washed five times in binding medium at room temperature and resuspended in 100 µl of the same medium. Phage were rescued by adding 1 ml of exponentially growing K91Kan *Escherichia coli* bacteria and incubating the mixture for 1 h at room temperature. Bacteria were diluted in 10 ml of LB medium supplemented with 0.2 µg/ml tetracycline and incubated for another 20 min at room temperature. Serial dilutions were plated on LB plates containing 40 µg/ml tetracycline, and plates were incubated at 37°C overnight before colonies were counted.

Phage binding specificity assay

The cell binding assay was performed with an input of 10^9 TU as described for the cell panning. The specificity was confirmed by adding CPRECESIC (SEQ ID NO:123) peptide to the binding medium in increasing concentrations. For phage binding on immunocaptured APA, wells were blocked for 1 h at room temperature with PBS/3% BSA and incubated with 10^9 TU for 1 h at room temperature in 50 µl PBS/3% BSA. After eight washes in PBS/1% BSA/0.01% Tween-20 and two washes in PBS,

phage were rescued by adding 200 µl of exponentially growing K91Kan *E. coli*. Each experiment was repeated at least three times.

In vivo tumor homing of APA-binding phage

MDA-MB-435-derived tumor xenografts were established in female nude mice 2 months old (Jackson Labs, Bar Harbor, Maine). Mice were anesthetized with Avertin and injected intravenously through the tail vein with 10^9 TU of the phage in a 200 µl volume of DMEM. The phage were allowed to circulate for 5 min, and the animals were perfused through the heart with 5 ml of DMEM. The tumor and brain were dissected from each mouse, weighed, and equal amounts of tissue were homogenized. The tissue homogenates were washed three times with ice-cold DMEM containing a proteinase inhibitor cocktail and 0.1% BSA. Bound phage were rescued and counted as described for cell panning. Fd-tet phage was injected at the same input as a control. The experiment was repeated twice. In parallel, part of the same tissue samples were fixed in Bouin solution, and imbedded in paraffin for preparation of tissue sections. An antibody to M-13 phage (Amersham-Pharmacia) was used for the staining.

Cell growth assay

HUVECs were seeded in 48-well plates (10^4 cells/well) and allowed to attach for 24 h in complete M199 medium. The cells were then starved in M199 medium containing 2% FCS for 24 h. CPRECESIC (SEQ ID NO:123) or control GACVRLSACGA (SEQ ID NO:124) peptide (1 mM) was added to the wells in medium containing 2% FCS and 10 ng/ml VEGF-A (R&D System, Abingdom, UK). After incubation for the indicated times, cells were fixed in 2.5% glutaraldehyde, stained with 0.1% crystal violet in 20% methanol, and solubilized in 10% acetic acid. All treatments were done in triplicate. Cell growth was evaluated by measuring the O.D. at 590 nm in a microplate reader (Biorad, Hercules, CA). A calibration curve was established and a linear correlation between O.D. and cell counts was observed between 10^3 and 10^5 cells.

Results

Cell panning with phage display select an APA-binding motif

To identify a peptide capable of binding to APA, cells were screened with a random peptide phage library. First, SK-RC-49 renal carcinoma cells, which do not express APA, were transfected with full-length APA cDNA to obtain a model of APA expression in the native conformation. APA expressed as a result of transfection was functionally active, as evidenced by an APA enzyme assay (not shown), but parental SK-RC-49 cells showed neither APA expression nor activity (not shown).

The $CX_3CX_3CX_3C$ phage library (10^{10} transducing units [TU]) was preadsorbed on parental SK-RC-49 cells to decrease nonspecific binding. Resuspended SK-RC-49/APA cells were screened with phage that did not bind to the parent cells. SK-RC-49/APA-bound phage were amplified and used for two consecutive rounds of selection. An increase in phage binding to SK-RC-49/APA cells relative to phage binding to SK-RC-49 parental cells was observed in the second and third rounds (not shown).

Subsequent sequencing of the phage revealed a specific enrichment of a peptide insert, CYNLCIRECESICGADGACWTWCADGCSRSC (SEQ ID NO:125), with a tandem repetition of the general library sequence $CX_3CX_3CX_3C$. This sequence represented 50% of 18 randomly selected phage inserts from round 2 and 100% of phage inserts from round 3. Four peptide inserts derived from round 2 shared sequence similarity with the tandem phage (Table 12, in bold font). Several other apparently conserved motifs were observed among round 2 peptides (Table 12, underlined or italicized). One of these overlapped in part with the tandem repeated sequence. A search for sequence homology of the selected peptides against human databases did not yield a significant match.

Table 12. APA-binding peptide sequences.

Peptide sequences [a]	Round 2 (%)	Round 3 (%)
CYNLCIRECESICGADGACWTWCADGCSRSC (SEQ ID NO:125)	50	100
CLGQCASICVNDC (SEQ ID NO:126)	5	-
CPKVCPRECESNC (SEQ ID NO:127)	5	-
CGTGCAVECEVVC (SEQ ID NO:128)	5	-
CAVACWADCQLGC (SEQ ID NO:129)	5	-
CSGLCTVQ*CLEGC* (SEQ ID NO:130)	5	-
CSMM*CLEGC*DDWC (SEQ ID NO:131)	5	-
OTHER	20	-

Selected phage inserts are specific APA ligands.

Phage displaying the peptide inserts CYNLCIRECESICGADGACWTWCADGCSRSC (SEQ ID NO:125), CPKVCPRECESNC (SEQ ID NO:127) or CLGQCASICVNDC (SEQ ID NO:126) were individually tested for APA binding. All three phage specifically bound to the

surface of SK-RC-49/APA cells (not shown), with a similar pattern of 6-fold enrichment relative to SK-RC-49 parental cells. Control, insertless phage showed no binding preference (not shown). CGTGCAV**ECE**VVC (SEQ ID NO:128) and the other phage selected in round 2 showed no selective binding to SK-RC-49/APA cells (data not shown). A soluble peptide, CPRECESIC (SEQ ID NO:123) containing a consensus sequence reproducing the APA-binding phage inserts was synthesized.

Binding assays were performed with CPKV**CPRECES**NC (SEQ ID NO:127) phage in the presence of the CPRECESIC (SEQ ID NO:123) peptide. Soluble CPRECESIC (SEQ ID NO:123) peptide competed with CPKV**CPRECES**NC (SEQ ID NO:127) phage for binding to SK-RC-49/APA cells, but had no effect on nonspecific binding to SK-RC-49 parental cells (not shown. The unrelated cyclic peptide GACVRLSACGA (SEQ ID NO:124) had no competitive activity (not shown). Binding of CYNL**CIRECESIC**GADGACWTWCADGCSRSC (SEQ ID NO:125) phage was also displaced by CPRECESIC (SEQ ID NO:123) peptide, but the binding of CLGQCA**SIC**VNDC (SEQ ID NO:126) phage was not affected (data not shown).

To further confirm the substrate specificity of the selected peptide inserts, APA was partially purified from APA-transfected cell extracts by immunocapture with mAb RC38. The APA protein immobilized on RC38-coated microwells was functional, as confirmed by enzyme assay (not shown). The CYNL**CIRECESIC**GADGACWTWCADGCSRSC (SEQ ID NO:125), CPKV**CPRECES**NC (SEQ ID NO:127), and CLGQCA**SIC**VNDC (SEQ ID NO:126) phage selectively bound immunocaptured APA, with a 10- to 12-fold enrichment compared to phage binding to RC38-immunocaptured cell lysates from SK-RC-49 parental cells (not shown).

APA-binding phage target tumors in vivo.

The ability of the identified peptide to home to tumors was evaluated, using nude mice implanted with human breast tumor xenografts as a model system. Phage were injected into the tail vein of tumor-bearing mice, and targeting was evaluated by

phage recovery from tissue homogenates. CPKVCPRECESNC (SEQ ID NO:127) phage was enriched 4-fold in tumor xenografts compared to brain tissue, which was used as a control (FIG. 22). Insertless phage did not target the tumors (FIG. 22). Neither CYNLCIRECESICGADGACWTWCADGCSRSC (SEQ ID NO:125) nor CLGQCASICVNDC (SEQ ID NO:126) phage showed any tumor-homing preference (data not shown).

The homing of CPKVCPRECESNC (SEQ ID NO:127) was confirmed by anti-M13 immunostaining on tissue sections (not shown). Strong phage staining was apparent in tumor vasculature but not in normal vasculature (not shown). Insertless phage did not bind to tumor vessels.

CPRECESIC (SEQ ID NO:123) is a specific inhibitor of APA activity.

To investigate the effect of CPRECESIC (SEQ ID NO:123) on APA enzyme activity, SK-RC-49/APA cells were incubated with the APA specific substrate α-glutamyl-p-nitroanilide in the presence of increasing concentrations of either CPRECESIC (SEQ ID NO:123) or control GACVRLSACGA (SEQ ID NO:124) peptides. Enzyme activity was evaluated by a colorimetric assay after 2 h incubation at 37°C. CPRECESIC (SEQ ID NO:123) inhibited APA enzyme activity, reducing the activity by 60% at the highest concentration tested (FIG. 23). The IC_{50} of CPRECESIC (SEQ ID NO:123) for enzyme inhibition was calculated to be 800 μM. CPRECESIC (SEQ ID NO:123) did not affect the activity of a closely related protease, aminopeptidase N (data not shown).

CPRECESIC (SEQ ID NO:123) inhibits migration and proliferation of endothelial cells.

The potential use of CPRECESIC (SEQ ID NO:123) peptide as an anti-angiogenic drug was determined. First, the effect of APA inhibition by CPRECESIC (SEQ ID NO:123) peptide *in vitro* on the migration and proliferation of human umbilical vein endothelial cells (HUVECs) stimulated with VEGF-A (10 ng/ml) was examined. The presence of functional APA on HUVECs was evaluated by enzyme

assay (not shown). At the highest concentration tested (1 mM), CPRECESIC (SEQ ID NO:123) peptide inhibited chemotaxis of HUVECs by 70% in a Boyden chamber assay (FIG. 24). At the same peptide concentration, cell proliferation was inhibited by 50% (FIG. 25). Lower concentrations of CPRECESIC (SEQ ID NO:123) peptide or the GACVRLSACGA (SEQ ID NO:124) control peptide had no significant effect on cell migration or proliferation (not shown).

CPRECESIC (SEQ ID NO:123) inhibits angiogenesis in vitro and in vivo

The inhibitory effect of CPRECESIC (SEQ ID NO:123) peptide in different *in vitro* and *in vivo* models of angiogenesis was examined. HUVECs plated on a three-dimensional matrix gel differentiate into a capillary-like structure, providing an *in vitro* model for angiogenesis. Increasing concentrations of CPRECESIC (SEQ ID NO:123) peptide resulted in a progressive impairment of the formation of this network (not shown). At a peptide concentration of 1 mM, vessel-like branching structures were significantly fewer and shorter, and as a result, the cells could not form a complete network organization (not shown). The control peptide GACVRLSACGA (SEQ ID NO:124) did not affect HUVEC morphogenesis (not shown).

A commonly used model of simplified *in vivo* angiogenesis is the chicken chorioallantoic membrane (CAM), in which neovascularization can be stimulated during embryonic development. An appropriate stimulus, adsorbed on a gelatin sponge, induces microvessel recruitment to the sponge itself, accompanied by remodeling and ramification of the new capillaries. Eight-day-old chicken egg CAMs were stimulated with VEGF-A alone (20 ng) or with VEGF-A plus CPRECESIC (SEQ ID NO:123) or GACVRLSACGA (SEQ ID NO:124) (1 mM) peptides. The CAMs were photographed at day 12. Neovascularization induced by VEGF-A was inhibited by CPRECESIC (SEQ ID NO:123) by 40% based on the number of capillaries emerging from the sponge (Table 13). The neovessels did not show the highly branching capillary structures typically seen after VEGF-A stimulation (not shown). Treatment with control peptide GACVRLSACGA (SEQ ID NO:124) or with lower

peptide concentrations of CPRECESIC (SEQ ID NO:123) had no effect on the number of growing vessels (not shown).

Table 13. CAM assay for angiogenesis

TREATMENT	BLOOD VESSEL NUMBERS
No VEGF-A	12.0 ± 2.82*
VEGF-A	57.0 ± 1.41*
VEGF-A + control	56.5 ± 2.12
VEGF-A + CPRECESIC (SEQ ID NO:123)	5.5 ± 1.41*

*p< 0.01 with the Student-Newman-Keuls test. The results are expressed as the mean and standard error from two independent experiments.

APA-deficient mice show impaired neovascularization

The ability of $APA^{+/-}$ and $APA^{-/-}$ null mice to undergo neovascularization was examined in a model of hypoxic retinopathy in premature mice. Induction of retinal neovascularization by relative hypoxia was already present in $APA^{+/-}$ mice compared to wild type mice (not shown). Neovascularization was almost undetectable in APA null mice (not shown). Neovascularization was quantified by counting vitreous protruding neovascular nuclei from 20 sections of hypoxic eyes. Significant induction of retinal neovascularization (16.17 ± 1.19 neovascular nuclei/eye section) was seen in the wild type mice on postnatal day 17 (P17) after 75% oxygen treatment from P7 to P12. Decreased amounts of neovascular nuclei were seen in the retinas of $APA^{+/-}$ (10.76 ± 1.03 neovascular nuclei/eye section) and APA null (4.25 ± 0.45 neovascular nuclei/eye section) mice on P17 after exposure to 75% oxygen from P7 to P12.

WHAT IS CLAIMED IS:

1. A method comprising
   a) injecting a subject with a phage display library;
   b) obtaining samples of one or more organs or tissues;
   c) producing thin sections of the samples; and
   d) recovering phage from the thin sections.
2. The method of claim 1, further comprising selecting one or more portions of a thin section by PALM (Positioning and Ablation with Laser Microbeams).
3. The method of claim 2, wherein the selected portion contains a specific cell type.
4. The method of claim 2, wherein the selected portion contains a homogenous population of cells.
5. The method of claim 3, wherein the cells are cancer cells.
6. The method of claim 1, wherein the phage are recovered by infecting bacteria with the phage.
7. The method of claim 1, wherein the phage are recovered by amplifying phage inserts and ligating the amplified inserts to phage DNA to produce new phage.
8. A method of preparing a phage display library comprising:
   a) immunizing a host animal with a target organ, tissue or cell type;
   b) obtaining mRNAs encoding antibodies from the host animal;
   c) preparing cDNAs from the mRNAs encoding antibodies; and
   d) preparing a phage display library from the cDNAs.
9. The method of claim 8, further comprising using antibody specific primers to amplify cDNAs that encode antibodies.
10. The method of claim 8, wherein the target organ, tissue or cell is diseased.

11. The method of claim 10, wherein the target comprises cancer cells.

12. The method of claim 8, further comprising: (i) injecting the phage display library into a subject; and (ii) recovering phage from one or more organs, tissues or cell types.

13. The method of claim 8, further comprising screening said library against a target protein or peptide.

14. A phage display library prepared by the method of claim 8.

15. A method of interfering with pregnancy comprising;

a) obtaining a peptide comprising at least three contiguous amino acids of a sequence selected from SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44 or SEQ ID NO:45; and

b) administering the peptide to a female subject.

16. The method of claim 15, wherein the subject is pregnant.

17. The method of claim 15, further comprising attaching an agent to the peptide.

18. A method of delivering an agent to a fetus comprising:

a) obtaining a peptide comprising at least three contiguous amino acids of a sequence selected from SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44 or SEQ ID NO:45;

b) attaching the peptide to an agent; and

b) administering the peptide to a pregnant subject.

19. The method of claims 17 or 18, wherein the agent is a drug, a pro-apoptotic agent, an anti-angiogenic agent, an enzyme, a hormone, a cytokine, a growth factor, a cytotoxic agent, a peptide, a protein, an antibiotic, an antibody, a Fab fragment of an antibody, an imaging agent, an antigen, a survival factor, an anti-apoptotic agent, a hormone antagonist, a virus, a bacteriophage, a bacterium, a liposome, a microparticle, a microdevice, a cell or an expression vector.

20. A method of targeting delivery to adipose tissue comprising:

a) obtaining a targeting peptide comprising an amino acid sequence of at least three contiguous amino acids selected from SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54 or SEQ ID NO:55;

b) attaching the peptide to an agent to form a complex; and

c) administering the complex to a subject.

21. The method of claim 20, further comprising inducing weight loss in said subject.

22. An isolated peptide of 100 amino acids or less in size, comprising at least 3 contiguous amino acids of a sequence selected from any of SEQ ID NO:5 through SEQ ID NO:45, SEQ ID NO:47 through SEQ ID NO:121, SEQ ID NO:123 and SEQ ID NO:125 through SEQ ID NO:250.

23. The isolated peptide of claim 22, wherein said peptide is 50 amino acids or less in size.

24. The isolated peptide of claim 22, wherein said peptide is 25 amino acids or less in size.

25. The isolated peptide of claim 22, wherein said peptide is 10 amino acids or less in size.

26. The isolated peptide of claim 22, wherein said peptide is 7 amino acids or less in size.

27. The isolated peptide of claim 22, wherein said peptide is 5 amino acids or less in size.

28. The isolated peptide of claim 22, wherein said peptide comprises at least 5 contiguous amino acids of a sequence selected from any of SEQ ID NO:5

through SEQ ID NO:45, SEQ ID NO:47 through SEQ ID NO:121, SEQ ID NO:123 and SEQ ID NO:125 through SEQ ID NO:250.

29. The isolated peptide of claim 22, wherein said peptide is attached to a molecule.

30. The isolated peptide of claim 29, wherein said molecule is a drug, a chemotherapeutic agent, a radioisotope, a pro-apoptosis agent, an anti-angiogenic agent, a hormone, a cytokine, a growth factor, a cytotoxic agent, a peptide, a protein, an antibiotic, an antibody, a Fab fragment of an antibody, an imaging agent, survival factor, an anti-apoptotic agent, a hormone antagonist or an antigen.

31. The isolated peptide of claim 30, wherein said pro-aptoptosis agent is selected from the group consisting of gramicidin, magainin, mellitin, defensin, cecropin, $(KLAKLAK)_2$ (SEQ ID NO:1), $(KLAKKLA)_2$ (SEQ ID NO:2), $(KAAKKAA)_2$ (SEQ ID NO:3) and $(KLGKKLG)_3$ (SEQ ID NO:4).

32. The isolated peptide of claim 30, wherein said anti-angiogenic agent is selected from the group consisting of thrombospondin, angiostatin5, pigment epithelium-drived factor, angiotensin, laminin peptides, fibronectin peptides, plasminogen activator inhibitors, tissue metalloproteinase inhibitors, interferons, interleukin 12, platelet factor 4, IP-10, Gro-ß, thrombospondin, 2-methoxyoestradiol, proliferin-related protein, carboxiamidotriazole, CM101, Marimastat, pentosan polysulphate, angiopoietin 2 (Regeneron), interferon-alpha, herbimycin A, PNU145156E, 16K prolactin fragment, Linomide, thalidomide, pentoxifylline, genistein, TNP-470, endostatin, paclitaxel, Docetaxel, polyamines, a proteasome inhibitor, a kinase inhibitor, a signaling peptide, accutin, cidofovir, vincristine, bleomycin, AGM-1470, platelet factor 4 and minocycline.

33. The isolated peptide of claim 30, wherein said cytokine is selected from the group consisting of interleukin 1 (IL-1), IL-2, IL-5, IL-10, IL-11, IL-12, IL-18,

interferon-γ (IF-γ), IF-α, IF-ß, tumor necrosis factor-α (TNF-α), or GM-CSF (granulocyte macrophage colony stimulating factor).

34. The isolated peptide of claim 22, wherein said peptide is attached to a macromolecular complex.

35. The isolated peptide of claim 34, wherein said complex is a virus, a bacteriophage, a bacterium, a liposome, a microparticle, a magnetic bead, a yeast cell, a mammalian cell or a cell.

36. The isolated peptide of claim 34, wherein said peptide is attached to a eukaryotic expression vector.

37. The isolated peptide of claim 36, wherein said vector is a gene therapy vector.

38. The isolated peptide of claim 22, wherein said peptide is attached to a solid support.

39. A composition comprising the isolated peptide of claim 22 in a pharmaceutically acceptable carrier.

40. The composition of claim 39, wherein the isolated peptide is attached to a molecule or a macromolecular complex.

41. The isolated peptide of claim 22, wherein said sequence is selected from any of SEQ ID NO:5 through SEQ ID NO:19.

42. The isolated peptide of claim 22, wherein said sequence is selected from any of SEQ ID NO:20 through SEQ ID NO:38.

43. The isolated peptide of claim 22, wherein said sequence is selected from any of SEQ ID NO:210 through SEQ ID NO:234.

44. The isolated peptide of claim 22, wherein said sequence is selected from any of SEQ ID NO:56 through SEQ ID NO:68.

45. The isolated peptide of claim 22, wherein said sequence is selected from any of SEQ ID NO:69 through SEQ ID NO:88.

46. The isolated peptide of claim 22, wherein said sequence is selected from any of SEQ ID NO:235 through SEQ ID NO:250.

47. The isolated peptide of claim 22, wherein said sequence is selected from SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91 or SEQ ID NO:92.

48. A kit comprising the isolated peptide of claim 22 and a control peptide, each in a container.

49. An antibody that selectively binds to an isolated peptide, the peptide comprising at least three contiguous amino acids selected from any of SEQ ID NO:5 through SEQ ID NO:45, SEQ ID NO:47 through SEQ ID NO:121, SEQ ID NO:123 and SEQ ID NO:125 through SEQ ID NO:250.

50. A method comprising;

a) injecting a subject with a phage display library;

b) recovering at least one sample of at least one organ, tissue or cell type;

c) separating the sample into isolated cells or clumps of cells;

d) centrifuging the cells through an organic phase to form a pellet; and

e) recovering phage from the pellet.

51. The method of claim 50, further comprising preselecting the phage display library against a different organ, tissue or cell type.

52. A gene therapy vector, wherein the vector expresses a targeting peptide sequence as part of a surface protein, the targeting peptide comprising at least three contiguous amino acids selected from any of SEQ ID NO:5 through SEQ ID NO:45, SEQ ID NO:47 through SEQ ID NO:121, SEQ ID NO:123 and SEQ ID NO:125 through SEQ ID NO:250.

53. A method of targeting delivery to an organ or tissue, comprising:

a) obtaining a peptide according to claim 22;

b) attaching the peptide to an agent; and

c) administering the agent to a subject.

54. The method of claim 53, wherein the subject is a human or a mouse.

55. The method of claim 53, wherein the agent is a drug, a chemotherapeutic agent, a radioisotope, a pro-apoptosis agent, an anti-angiogenic agent, an enzyme, a hormone, a cytokine, a growth factor, a cytotoxic agent, a peptide, a protein, an antibiotic, an antibody, a Fab fragment of an antibody, an imaging agent, an antigen, a survival factor, an anti-apoptotic agent, a hormone antagonist, a virus, a bacteriophage, a bacterium, a liposome, a microparticle, a magnetic bead, a microdevice, a yeast cell, a mammalian cell, a cell or an expression vector.

56. The method of claim 53, wherein the agent is an imaging agent.

57. The method of claim 56, further comprising obtaining an image of the subject.

58. The method of claim 57, wherein the image is diagnostic for a disease.

59. The method of claim 58, wherein the disease is cancer, arthritis, diabetes, inflammatory disease, atherosclerosis, autoimmune disease, bacterial infection, viral infection, cardiovascular disease or degenerative disease.

60. The method of claim 53, wherein the organ or tissue is bone marrow, prostate, prostate cancer, ovary, ureter, placenta, adipose, spleen, angiogenic tissue or ascites.

61. A method of targeting delivery to prostate cancer comprising:

a) obtaining a targeting peptide comprising at least three contiguous amino acids selected from any of SEQ ID NO:20 through SEQ ID NO:38;

b) attaching the peptide to a therapeutic agent to form a complex; and

c) administering the complex to a subject with prostate cancer.

62. A method of diagnosing prostate cancer comprising:

a) obtaining a targeting peptide comprising at least three contiguous amino acids selected from any of SEQ ID NO:20 through SEQ ID NO:38;

b) administering the peptide to a subject suspected of having prostate cancer; and

c) detecting the peptide bound to prostate cancer cells.

63. A method of identifying targeting peptides to angiogenic tissue comprising:

a) inducing hypoxia in a neonatal subject;

b) administering a phage display library to the subject; and

c) recovering phage from the retina of the subject.

64. A method of inducing apoptosis in a cell comprising:

a) obtaining a targeting peptide comprising at least three contiguous amino acids selected from any of SEQ ID NO:93 through SEQ ID NO:121;

b) attaching the peptide to a permeabilizing agent to form a complex; and

c) administering the complex to the cell.

65. The method of claim 64, wherein the permeabilizing agent is selected from a peptide with an amino acid sequence of SEQ ID NO:122 or HIV Tat protein.

66. The method of claim 64, wherein the targeting peptide has the amino acid sequence of SEQ ID NO:112.

67. A method of inducing apoptosis in a cell comprising:

a) attaching Annexin V to a permeabilizing agent to form a complex; and

b) administering the complex to the cell.

68. The method of claim 67, wherein the permeabilizing agent is selected from a peptide with an amino acid sequence of SEQ ID NO:122 or HIV Tat protein

69. A method of modulating angiogenesis comprising:

a) obtaining a peptide comprising at least three contiguous amino acids selected from SEQ ID NO:93 through SEQ ID NO:131; and

b) administering the peptide to a subject.

70. The method of claim 69 wherein the subject has a tumor and the peptide inhibits tumor growth or survival.

71. The method of claim 69, wherein the peptide is attached to an agent.

72. The method of claim 71, wherein the agent is thrombospondin, angiostatin5, pigment epithelium-drived factor, angiotensin, laminin peptides, fibronectin

peptides, plasminogen activator inhibitors, tissue metalloproteinase inhibitors, interferons, interleukin 12, platelet factor 4, IP-10, Gro-ß, thrombospondin, 2-methoxyoestradiol, proliferin-related protein, carboxiamidotriazole, CM101, Marimastat, pentosan polysulphate, angiopoietin 2 (Regeneron), interferon-alpha, herbimycin A, PNU145156E, 16K prolactin fragment, Linomide, thalidomide, pentoxifylline, genistein, TNP-470, endostatin, paclitaxel, accutin, cidofovir, vincristine, bleomycin, AGM-1470, platelet factor 4 or minocycline.

73. The method of claim 69, wherein the peptide has anti-angiogenic activity.

74. The method of claim 69, wherein the peptide has pro-angiogenic activity.

75. The method of claim 73, further comprising administering the peptide to a subject with ischemia.

76. The method of claim 73, further comprising administering the peptide to a subject with cardiovascular disease.

77. The method of claim 69, further comprising administering the peptide to a subject with cancer, arthritis, diabetes, cardiovascular disease, inflammation or macular degeneration.

78. A method of targeting delivery to an angiogenic tissue comprising:

a) obtaining a peptide comprising at least three contiguous amino acids selected from SEQ ID NO:123, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130 or SEQ ID NO:131;

b) attaching the peptide to a therapeutic agent to form a complex; and

b) administering the complex to a subject.

79. The method of claim 78, wherein the peptide has an amino acid sequence of SEQ ID NO:123.

80. The method of claim 78, wherein the angiogenic tissue is from a subject with cancer, arthritis, diabetes, cardiovascular disease, inflammation or macular degeneration.

81. A method of detecting receptors for endostatin or angiostatin comprising

a) obtaining a sample from a tissue or organ;

b) incubating the sample with endostatin or angiostatin; and

c) detecting the presence of endostatin or angiostatin bound to the sample.

82. The method of claim 81, wherein the sample is a thin section of a tissue or organ.

83. The method of claim 82, further comprising assessing specificity by inhibiting binding with a targeting peptide selective for endostatin or angiostatin.